Prevention and Management of Chronic Heart Failure with Electrical Therapy

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Sudden cardiac death is responsible for >40% of patients with heart failure losing their lives. Thus, the prevention of life-threatening cardiac arrhythmias is a major goal in the management of heart failure. In several randomized clinical trials, electrical therapy with the implantable cardioverter defibrillator (ICD) has proved superior to medical antiarrhythmic therapy in both the secondary and primary prevention of sudden cardiac death in patients with reduced left ventricular function. In addition to the severity of left ventricular dysfunction, the etiology of the cardiomyopathy appears to be a determinant in the benefit derived from this form of electrical therapy. Whereas patients with ischemic cardiomyopathy clearly show improved survival with ICD therapy, outcome data in patients with nonischemic cardiomyopathy are less convincing. The major challenge lies in the risk stratification of patients with heart failure for arrhythmic death. Catheter ablation is another form f electrical therapy that can help in the treatment of patients with heart failure. In patients with a tachycardia-mediated cardiomyopathy because of drug-refractory atrial fibrillation with rapid ventricular response, catheter ablation of the atrioventricular node and pacemaker implantation can effectively restore a physiologic heart rate, often with dramatic regression of left ventricular dysfunction. In patients with frequent ICD therapies because of frequent recurrences of ventricular tachyarrhythmias, catheter ablation of ventricular tachycardia can be an effective adjunctive therapy. New catheter ablation techniques and new atrial pacing algorithms can also significantly reduce the atrial fibrillation burden in patients with heart failure who are particularly susceptive to decompensation because of atrial fibrillation. Pacing for hemodynamic benefit in heart failure has evolved from dual-chamber pacing modes with optimized atrioventricular delay to biventricular pacing resulting in cardiac resynchronization. This new treatment modality for advanced heart failure has been shown to result in significant symptomatic and hemodynamic improvement. ©2003 by Excerpta Medica, Inc.

Am J Cardiol 2003;91(suppl):62F–73F

Cardiac arrhythmias are a common finding in patients with heart failure and are related to the severity of heart disease. Symptomatic or incidentally found arrhythmias can be the initial presentation of an underlying cardiomyopathy leading to further cardiac evaluation. Sudden cardiac death accounts for most cardiac deaths in patients with mild-to-moderate heart failure and for about 33% of deaths in advanced heart failure (Figure 1).[1,2] Unfortunately, in about 10% of sudden death cases, a life-threatening arrhythmia is the first manifestation of heart disease. Complex ventricular tachyarrhythmias, including nonsustained ventricular tachycardia (VT), have been described in up to 85% of patients with congestive heart failure and are associated with increased mortality (Table 1).[3–5] Ventricular arrhythmias are much more common in patients with nonischemic dilated cardiomyopathy compared with patients with coronary disease, and their prevalence varies largely in results of repeated Holter monitoring. In patients with coronary disease, the incidence of nonsustained VT is about 10%, whereas the incidence in patients with nonischemic dilated cardiomyopathy is 30% to 40%, and in New York Heart Association (NYHA) functional class III or IV, it is as great as 70%. In patients with ischemic cardiomyopathy, nonsustained VT is a relatively specific predictor of sudden cardiac death and is amenable to defibrillator therapy. In contrast, in patients with nonischemic dilated cardiomyopathy, the presence of nonsustained VT may not specifically predict sudden cardiac death because of arrhythmias, but it is more a marker of increased mortality because of progressive pump failure.[4–7] The frequency of ventricular tachyarrhythmias has been shown to correlate with indices of left ventricular size and pressure, consistent with the hypothesis of stretch-induced arrhythmias.[8]

Atrial fibrillation is another frequent arrhythmia seen in patients with heart failure. The prevalence of atrial fibrillation increases with the severity of heart failure: 4% in patients with NYHA class I, 10% to 30% in NYHA class II to III, and up to 50% in NYHA class IV.[9–12] Patients with reduced left ventricular function often have worsening heart failure associated with atrial fibrillation because of the loss of atrial contraction and/or rapid ventricular rate. In some patients, persistent rapid ventricular rates during atrial fibrillation may cause a tachycardia-mediated cardiomyopathy that is often reversible after adequate rate control.[13] The increased mortality observed with atrial fibrillation probably reflects increased severity of the underlying heart disease and adverse effects of antiarrhythmic drugs, because medical treatment of atrial fibrillation has not been shown to improve mortality.[14,15] Atrial fibrillation may also be proarrhythmic in patients at risk for ventricular tachyar-

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0002-9149/03/$ – see front matter
doi:10.1016/S0002-9149(02)03340-4

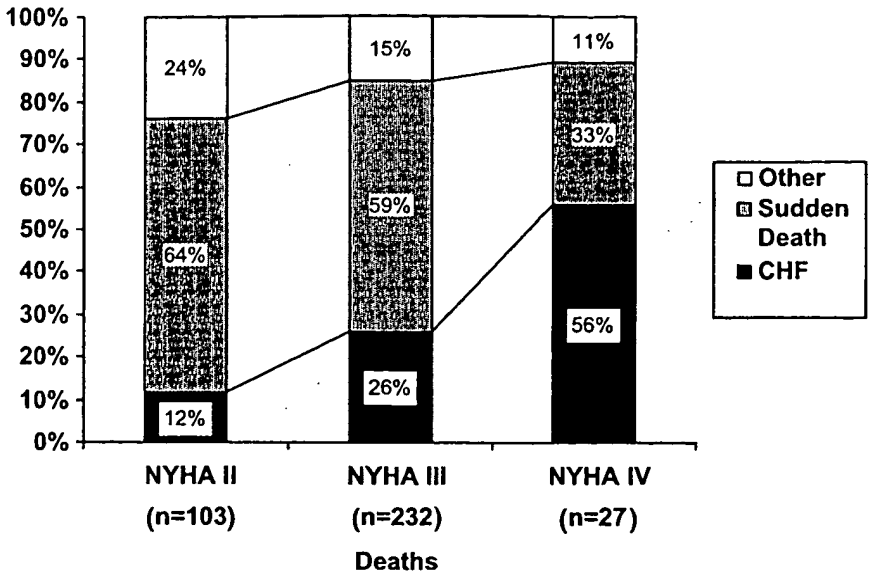


FIGURE 1. Mode of death and severity of heart failure. With mild-to-moderate heart failure, sudden cardiac death is more common than death from pump failure and accounts for most deaths. With increasing severity of heart failure, death from pump failure predominates. CHF = congestive heart failure; NYHA = New York Heart Association. (Reprinted with permission from *Lancet*.[2])

TABLE 1 Incidence of Ventricular Arrhythmias in the Prospective Milrinone Survival Evaluation (PROMISE) Trial During 24-Hour Ambulatory Electrocardiographic Monitoring*

Patients (n)	1,080
Age (yr)	64 ± 11
CAD (%)	54
NYHA III/IV (%)	58/42
Ejection fraction	0.21 ± 0.07
PVCs >30/hr (%)	60
Ventricular couplets (%)	85
NSVT, total (%)	61
NSVT >5 episodes (%)	29
NSVT >10 beats (%)	10

CAD = coronary artery disease; NYHA = New York Heart Asociation; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular complex.
*Percentages indicate the percent of patients in whom an arrhythmia was found.

rhythmias as demonstrated in patients with implantable cardioverter defibrillators (ICDs) with extended dual-chamber diagnostic capabilities.[16]

The electrophysiologic substrates associated with cardiac arrhythmias in patients with heart failure are varied and include (1) alterations in myocardial architecture, (2) spatial and temporal inhomogeneity of action potential duration, (3) remodeling of ion channels, and (4) changes in autonomic regulation. Myocardial ischemia, electrolyte abnormalities, drugs, and autonomic fluctuations can act as triggers in this susceptible milieu, leading to arrhythmias.[1] The etiology of heart failure is a determinant in the mechanism of arrhythmias and their inducibility during electrophysiologic evaluation. Reentrant sustained VTs around large ventricular scars are characteristic for patients with ischemic cardiomyopathy and prior myocardial infarction, and they are reproducible in 80% to 90% of patients presenting with this problem. In patients with coronary disease who present with nonsustained VT, inducibility ranges from 30% to 40%.[17] In contrast, in patients with nonischemic cardiomyopathy, this percentage ranges from 10% to 15%.[18,19] Although patients with nonischemic cardiomyopathy and with inducible arrhythmias have a worse prognosis than those without inducible arrhythmias, noninducibility of VT in these patients does not imply a benign prognosis. Focal nonreentrant mechanisms, such as triggered activity or abnormal automaticity, appear responsible for a large proportion of VTs in these patients, and up to 50% of tachycardias may be epicardial in origin.[20] There is considerable overlap among these patient populations, and all mechanisms of arrhythmias can be observed in any patient with congestive heart failure.

The development of arrhythmias may, in turn, precipitate or intensify heart failure through several mechanisms:

1. Tachyarrhythmias, most commonly atrial fibrillation, reduce the time available for ventricular fill-

ing, increase myocardial oxygen demands, and may also directly impair contractility in failing human myocardium caused in part by a negative force-frequency relation. If persistent, tachyarrhythmias may cause a reversible dilated cardiomyopathy.[13]

2. Marked bradycardia in a patient with underlying heart disease may decrease cardiac output because stroke volume cannot adequately increase to maintain cardiac output.
3. Dissociation between atrial and ventricular contraction, which can occur with prolonged atrioventricular conduction, leads to a loss of the atrial contribution to ventricular filling, resulting in diminished cardiac output and increased atrial pressure. This loss is particularly deleterious in patients with impaired ventricular filling because of decreased ventricular compliance.
4. Prolonged intraventricular conduction, which may be seen in patients with prolonged QRS interval duration, impairs myocardial performance because of loss of the normal synchronicity of ventricular contraction.

The most effective treatment for bradyarrhythmias has always been pacing therapy. Tachyarrhythmias, on the other hand, used to be the target of antiarrhythmic drugs. However, based on the results of the Cardiac Arrhythmia Suppression Trial (CAST) and other antiarrhythmic drug trials, it became evident that these agents may increase overall mortality or have, at best, a neutral effect on adverse outcomes.[21]

Therefore, electrical therapies for tachyarrhythmias in heart failure are gaining importance. With the advent of cardiac resynchronization therapy, the indications for cardiac pacing have been considerably expanded to include therapy of heart failure in addition to treatment of arrhythmias. The effectiveness and indications for electrical therapy for treatment of arrhythmias in heart failure will be discussed in this article. The benefits and mechanisms of cardiac resynchronization therapy will be discussed elsewhere in this supplement.[22]

IMPLANTABLE CARDIAC DEFIBRILLATORS

With recent advances in heart failure management, the functional capacity and quality of life of these patients, once stabilized on medical therapy, are frequently acceptable. The major risk is not hemodynamic decompensation, which generally occurs slowly in adult patients under careful supervision, but instead, sudden death. Sudden death accounts for 28% to 68% of all deaths in patients with heart failure and is attributed mostly to VT or ventricular fibrillation (VF).[1,2] ICDs have been shown to effectively terminate VT or VF, with a success rate close to 100%.[23] Because of advances in capacitor and lead technology, implantation of newer ICDs is associated with an operative mortality of <1% and acceptable longevity and cosmetic results. The questions that several recent randomized trials have attempted to answer are whether the high antiarrhythmic effectiveness and low morbidity and mortality associated to ICD therapy will translate into improved survival of patients at risk for sudden cardiac death.

Secondary prevention of sudden cardiac death: In 3 major randomized trials, the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, the Cardiac Arrest Study Hamburg (CASH), and the Canadian Implantable Defibrillator Study (CIDS), the benefit of ICD therapy in the prevention of sudden cardiac death in patients resuscitated from cardiac arrest or with documented hemodynamically significant VTs has been demonstrated.[24–26] In these trials, ICD therapy was compared with antiarrhythmic therapy, mostly amiodarone; there was no control arm in these studies because of ethical concerns. The vast majority (>90%) of patients in these trials had structural heart disease, and the mean ejection fraction was 0.35. Tables 2 and 3 summarize the patient characteristics and results of these 3 trials in a pooled analysis.[27] In these trials, <20% of patients had nonischemic dilated cardiomyopathy (as opposed to a history of coronary artery disease). Subgroup analysis showed that patients with nonischemic dilated cardiomyopathy derive the same benefit from devices as do other groups of patients who have had a cardiac arrest or VT.[28] Follow-up data on patients who received an ICD showed that 42% to 60% of patients received shocks for VT or VF during a follow-up period of 2 to 3 years. Mortality was 20% to 30% during this time frame (Figure 2). Left ventricular ejection fractions <0.25, class III or IV heart failure, and cluster shocks (>3 in a 24-hour period) were associated with increased mortality in this population.[29] The greatest benefit of ICD therapy was seen in patients with a left ventricular ejection fraction ≤0.30.[30]

Primary prevention of sudden cardiac death: Patients with heart failure who present with hemodynamically significant sustained ventricular tachyarrhythmias or who have survived a cardiac arrest episode constitute only the tip of the iceberg of patients at risk for sudden cardiac death. Survival to discharge from the hospital after a cardiac arrest episode remains extremely low (1.5% to 28%) and depends largely on the effectiveness and availability of emergency medical services capable of defibrillating the patient within a few minutes of such an event.[1] Therefore, identification and treatment of patients at risk for sudden cardiac death before a catastrophic event is desirable (primary prevention).

In 3 major randomized primary prevention trials, it has been shown that ICD therapy reduces mortality in patients with a severely reduced left ventricular ejection fraction (≤0.30 to 0.40) because of chronic coronary artery disease. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) included 196 patients with a myocardial infarction ≥3 weeks before study entry who had an ejection fraction ≤0.35 and a documented episode of asymptomatic, nonsustained VT.[31] All eligible patients had an electrophysiologic study, and only those patients with inducible sustained VT (>15 seconds) that was not suppressed by procainamide were included. Patients were randomized

TABLE 2 Defibrillators in the Secondary Prevention of Sudden Cardiac Death: Features of 3 Trials

	AVID (1993–1997)	CASH (1986–1997)	CIDS (1990–1997)
Medical treatment	Amiodarone, sotalol	Amiodarone	Amiodarone
Eligibility	VT, VF	VF	VT, VF, syncope
Mean follow-up (yr)	1.51	4.48	2.96
Patients (n)			
Medical therapy	509*	92	331
ICD	507	99	328
Total follow-up (patient-yr)			
Medical therapy	738	373	957
ICD	801	483	995
Deaths (n)	202	72	181

AVID = Antiarrhythmics Versus Implantable Defibrillators Trial; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

*Twelve patients were discharged on sotalol, the rest on amiodarone.

TABLE 3 Defibrillators in the Secondary Prevention of Sudden Cardiac Death: Pooled Database Analysis of 3 Trials*

	ICD (n = 934)	Amiodarone (n = 932)
Age (yr)	63 ± 11	64 ± 10
Male sex	81	82
LVEF	0.34 ± 0.15	0.33 ± 0.14
NYHA class III or IV	9	12
Prior myocardial infarction	69	69
Nonischemic cardiomyopathy	12	13
No heart disease	4	3
Presenting arrhythmia		
VF	51	52
VT	44	43
Syncope	5	4
Discharged on β-blocker	42	19
Discharged on ACE inhibitor	63	64
Discharged on aspirin	51	51

*Antiarrhythmics Versus Implantable Defibrillators trial (AVID), Cardiac Arrest Study Hamburg (CASH), and Canadian Implantable Defibrillator Study (CIDS).

ACE = angiotensin-converting enzyme; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

within 30 days to implantation of a defibrillator or conventional therapy (74% received amiodarone) at the discretion of the treating physician. Over an average follow-up period of 2 years, a 54% reduction in total mortality was observed in the patients randomized to the ICD versus conventional therapy. The use of β-blockade, amiodarone, or other antiarrhythmic drugs had no effect on the hazard ratio.

The Multicenter Unsustained Tachycardia Trial (MUSTT) enrolled 2,202 patients with coronary artery disease, a left ventricular ejection fraction ≤0.40, and nonsustained VT.[32] A total of 767 (35%) of the cohort had inducible sustained VT; 704 of them were randomized to either conventional therapy that included β-blockers and angiotensin-converting enzyme inhibitors, or electrophysiologically guided therapy. In the group randomized to electrophysiologically guided therapy, antiarrhythmic drug therapy was initiated in addition to β-blockers and angiotensin-converting enzyme inhibitors. Patients not responding to antiarrhythmic drug therapy on electrophysiologic study were treated with an ICD. The primary end point, arrhythmic death or cardiac arrest, occurred in 32% randomized to no antiarrhythmic drug therapy versus 25% randomized to electrophysiologically guided therapy, which represents a 27% reduction in risk at 5 years. This benefit in patients randomized to electrophysiologically guided therapy was solely because of improved survival in patients receiving an ICD, who had a 76% risk reduction in arrhythmic death and 50% risk reduction in overall mortality. In contrast, patients with inducible VT receiving antiarrhythmic agents had a worse outcome than patients randomized to receive no antiarrhythmic therapy.

The second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) studied prophylactic

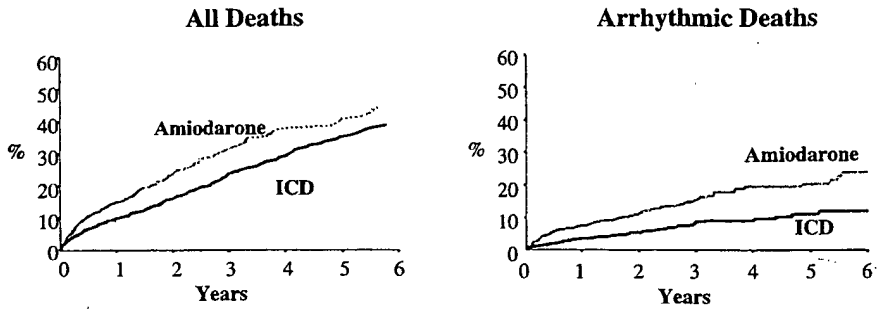
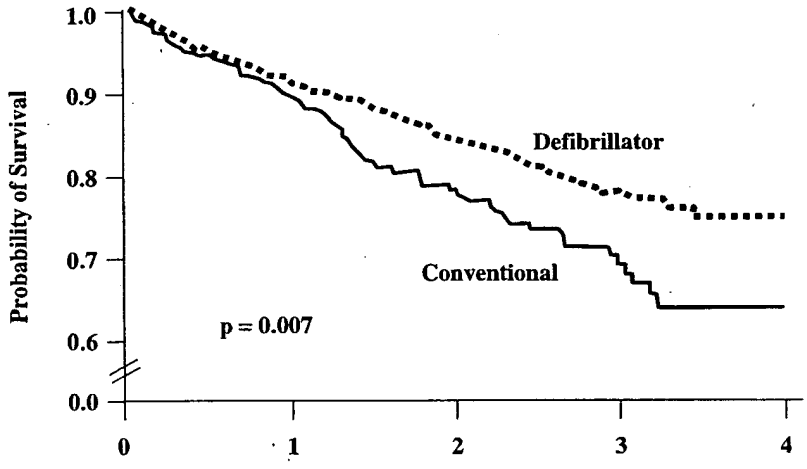


FIGURE 2. Cumulative risk of fatal events in a pooled database of secondary prevention trials (Antiarrhythmics Versus Implantable Defibrillator trial [AVID], Cardiac Arrest Study Hamburg [CASH], and Canadian Implantable Defibrillator Study [CIDS]. Implantations of an implantable cardioverter defibrillator (ICD) was associated with a 27% risk reduction in all deaths and 50% risk reduction in arrhythmic deaths compared with amiodarone therapy. (Reprinted with permission from *Eur Heart J.*[27])



No. at Risk					
Defibrillator	742	502 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

FIGURE 3. Benefit of implantable cardioverter defibrillator (ICD) therapy for primary prevention of sudden cardiac death. In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), implantation of an ICD was associated with a 31% risk reduction of overall mortality compared with conventional therapy in patients with ischemic cardiomyopathy and a left ventricular ejection fraction ≤0.30. Numbers in parentheses indicate probability of survival at respective years. (Reprinted with permission from *N Engl J Med.*[33])

ICDs in the broadest group of patients to date.[33] It included 1,232 patients with a history of myocardial infarction ≥1 month and an ejection fraction ≤0.30; patients were not required to have spontaneous arrhythmias or electrophysiologic testing for risk stratification to be eligible for participation. They were randomized to an ICD plus optimal medical therapy or medical therapy alone, which consisted of β-blocker therapy in about 70% of patients and angiotensin-converting enzyme inhibitors in >70% of patients. Over a mean follow-up time of 20 months, those in the ICD group had a mortality rate of 14.2% versus 19.8% of those randomized to medical therapy (relative risk reduction, 31%; p = 0.016; Figure 3). All 3 trials showed a significant reduction in overall mortality and arrhythmic mortality, which was equal to or exceeded the benefit observed in secondary-prevention trials (Figure 4).

The only randomized trial in patients with ischemic cardiomyopathy that showed no benefit of prophylactic ICD implantation was the Coronary Artery Bypass Graft-Patch (CABG-Patch) trial, which was undertaken to determine the effects of prophylactic implantation of an ICD at the time of coronary artery bypass surgery.[34] The 900 randomized patients had clinically indicated coronary bypass graft, left ventricular dysfunction (ejection fraction ≤0.35), and abnormal findings on signal-averaged electrocardiograms. Patients were randomized to an ICD or no device at the time of their bypass surgery. No antiarrhythmic drug therapy was administered for asymptomatic ventricular arrhythmias. After an average follow-up time of 32

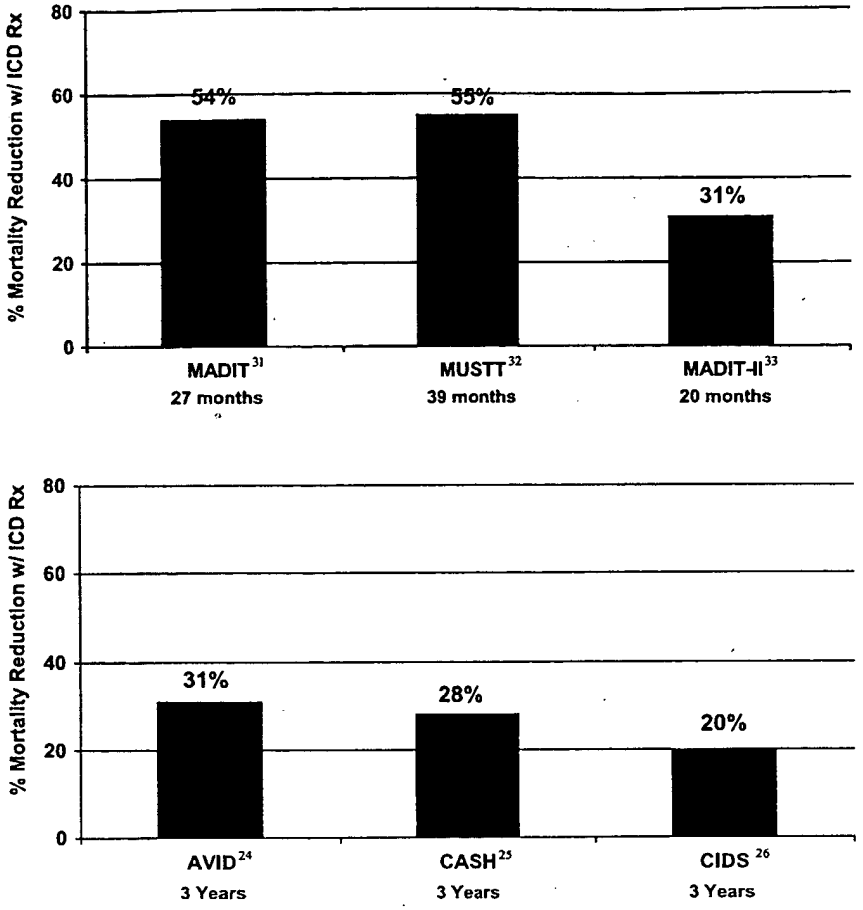


FIGURE 4. Reduction of overall mortality with implantable cardioverter-defibrillator (ICD) therapy (Rx) in primary- (*top*) and secondary-prevention (*bottom*) trials of sudden cardiac death. The ICD mortality reductions in primary-prevention trials are equal to or greater than those in secondary-prevention trials. AVID = Antiarrhythmics Versus Implantable Defibrillator trial; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MUSST = Multicenter Sustained Tachycardia Trial.

months, no significant difference in survival was observed between the 2 groups. A lesson learned from CABG-Patch was the importance of evaluating and treating myocardial ischemia to reduce the risk of mortality in patients with ischemic cardiomyopathy.

In contrast to patients with ischemic cardiomyopathy, the benefit of prophylactic implantation of ICDs in patients with nonischemic cardiomyopathy has not been established. The Amiodarone Versus Implantable Defibrillator Randomized Trial (AMIOVIRT) enrolled 200 patients with nonischemic dilated cardiomyopathy, an ejection fraction ≤0.35, and nonsustained VT. Patients were then randomized to an ICD or amiodarone.[35] No difference in survival was observed between the ICD and amiodarone groups. In both arms, 3-year survival was about 80%. The Cardiomyopathy Arrhythmia Trial (CAT) included 104 patients with recent nonischemic dilated cardiomyopathy and an ejection fraction <0.35 who were randomized to an ICD or to no device.[36] There was no difference in survival between the active treatment and control groups at 2, 4, and 6 years (92%, 86%, and 73% vs 93%, 80%, and 68%, respectively; Figure 5). Overall mortality in CAT was low (about 30% at 6 years). Among patients receiving an ICD in this trial, patients who had appropriate VT detections and therapies during follow-up study (11 of 50 patients) had a survival rate of only 44% at 6 years compared with 83% in those without VT. This suggests that recurrent VT in this patient population is a marker of cardiac deterioration rather than an independent risk factor for sudden cardiac death preventable by ICDs. It is possible that the lack of survival benefit with ICD therapy was because of the low event rate in the control group in both trials. These trials were powered to detect an ICD benefit based on a much higher event rate in the control group. Earlier studies at the time these trials were designed suggested a mortality as high as 70% at 3 years in patients with nonischemic dilated cardiomyopathy. However, community-based contemporary studies and the results of recent heart failure trials have suggested a much lower mortality than previously believed (approximately 10% at 3 years and 20% at 5 years).[37] On the other hand, the lack of

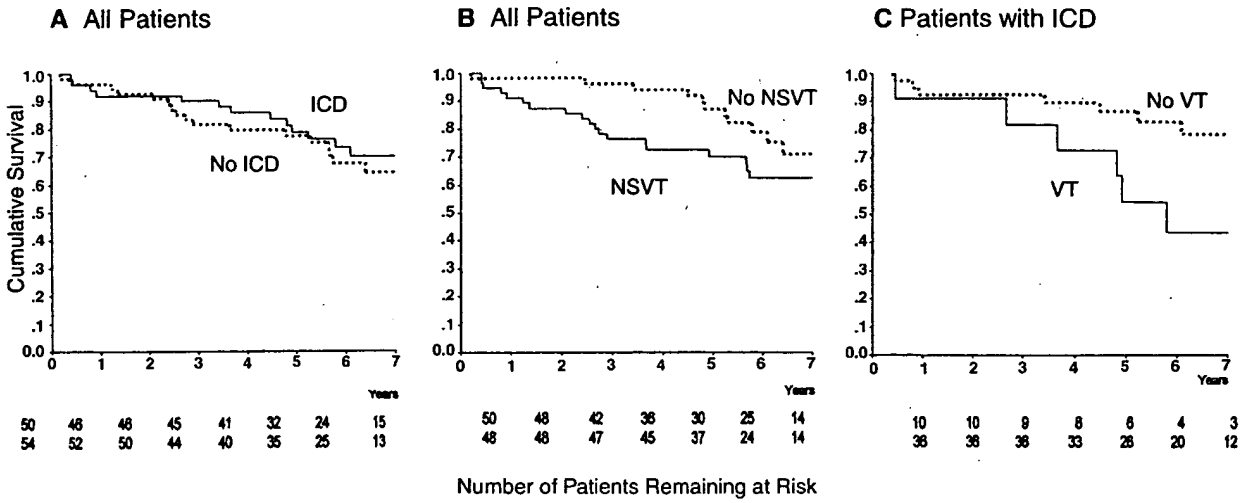


FIGURE 5. Implantable cardioverter-defibrillator (ICD) therapy in patients with nonischemic cardiomyopathy. (*A*) In the Cardiomyopathy Arrhythmia Trial (CAT), ICD therapy was not associated with improved survival in patients with recent-onset (≤9 months) nonischemic cardiomyopathy and an ejection fraction of ≤0.30. (*B*) Patients with nonsustained ventricular tachycardia (NSVT) at baseline had a worse prognosis than those without NSVT. (*C*) However, the presence of ventricular tachycardia (VT) was associated with increased mortality even in patients with implanted defibrillators, despite appropriate therapy by the device. (Reprinted with permission from *Circulation*.[36])

survival benefit in patients with appropriately treated fast VT or VF episodes by the ICD calls into question the concept that effective termination of hemodynamically significant ventricular tachyarrhythmias saves lives.

RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH

The most important independent predictor of sudden cardiac death (and overall mortality) in patients with heart failure is left ventricular systolic function. An ejection fraction ≤0.30 by itself in patients with coronary artery disease appears to justify prophylactic ICD implantation in patients in whom no coronary bypass surgery is planned.[33] In patients with ischemic heart disease and an ejection fraction ≤0.40, the presence of nonsustained VT identifies patients at risk who should undergo further electrophysiologic testing. In these patients, inducibility of sustained VT further identifies patients who may benefit from ICD implantation.[17] In patients with nonischemic dilated cardiomyopathy, nonsustained ventricular tachyarrhythmias are so common that they lose their specificity in predicting increased sudden death independent of the left ventricular ejection fraction. Syncope may be a valuable risk predictor in patients with nonischemic dilated cardiomyopathy.[38,39] The incidence of syncope ranges from 8% in patients with recently diagnosed nonischemic dilated cardiomyopathy referred for follow-up study to 24% in patients with advanced heart failure referred for transplantation. The mortality associated with syncope is estimated at 30% to 40% during 2 to 3 years of follow-up study. Retrospective studies of ICDs in patients with nonischemic dilated cardiomyopathy and syncope have demonstrated that the incidence of shocks was relatively high (30% to 40% of patients will receive a shock in the first 2 or 3 years), but the effect of ICDs on mortality was inconsistent.[39,40] In patients awaiting cardiac transplantation, ICD therapy has been associated with improved survival.[41] Other noninvasive predictors for sudden cardiac death are emerging, such as parameters of autonomic function (heart rate variability, baroreceptor sensitivity, T-wave alternans) and neurohumoral factors (brain natriuretic peptide).[1,19,42,43] In general, these parameters have a better negative predictive value than positive predictive value, despite being statistically significant risk stratifiers.

CATHETER ABLATION OF VENTRICULAR TACHYCARDIA

Although ICD therapy has revolutionized the treatment of VT—providing effective termination of VT or VF, regardless of etiology—it does not prevent recurrences. Patients with defibrillators may remain symptomatic with palpitations, syncope, and recurrent shocks. Pharmacologic treatment can help reduce recurrences. However, only a few antiarrhythmic agents (amiodarone, sotalol) are considered safe in patients with congestive heart failure, and their use is limited by incomplete efficacy or intolerability. Radiofrequency catheter ablation of VT provides a nonpharmacologic option for these patients to improve symptoms and quality of life. In contrast to supraventricular tachycardia, VT circuits in patients with structural heart disease are much more complex, and mapping of VT to identify an optimal region for ablation can be challenging. Initially, VT ablation was limited to patients with hemodynamically well-tolerated VTs with a single or very few stable morphologies, predominantly because of myocardial infarction–related scars.[44] Techniques combining sequential pace map-

ping and entrainment mapping were used with a 70% to 80% short-term success rate in this select group of patients.[45,46] Long-term follow-up study showed that about 90% of these patients remained free of arrhythmia recurrence after 1 year if no (clinical or nonclinical) VT remained inducible at a follow-up study a few days after ablation. In contrast, if any VT remained inducible, about 50% of patients had a recurrence of VT within 1 year.

More recently, emergence of 3-dimensional mapping technologies that can reconstruct and relate electrophysiologic characteristics to specific anatomy have enabled a "substrate mapping" approach that allows characterization of the reentry substrate during stable sinus rhythm, with minimal mapping during VT.[45,47,48] A diminished bipolar electrographic amplitude (<1.5 mV) has become accepted as a marker of scarred myocardium, and plots of electrogram amplitude, referred to as "voltage maps," can delineate the infarct region, which tends to be large. A combination of substrate mapping with arrhythmia mapping can identify the region of the scar that contains a potential reentry circuit, where catheter ablation would be most effective. Because the time spent mapping during VT is limited, this approach has made catheter ablation feasible in patients with hemodynamically poorly tolerated VTs and multiple VT morphologies, as well as select patients with nonischemic dilated cardiomyopathy.[49]

Currently, the role of VT ablation in patients with structural heart disease is adjunctive to ICD therapy because of concerns of persistent risk of sudden cardiac death. Analysis of stored electrograms in patients who received ICDs in the AVID trial showed that 15% of patients who had sustained monomorphic VT as their index arrhythmia also had VF not preceded by VT during a 2-year follow-up period.[50] Whether VT ablation as sole antiarrhythmic therapy is safe in select patients with structural heart disease remains to be determined.

ELECTRICAL THERAPY FOR PREVENTION AND TREATMENT OF ATRIAL TACHYARRHYTHMIAS

In patients with atrial fibrillation or other supraventricular tachyarrhythmias, electrical treatment options include (1) ablate and pace (ie, catheter ablation of the atrioventricular node and ventricular pacing), (2) curative catheter ablation of atrial fibrillation or supraventricular tachycardia, (3) specific pacing algorithms and pacing sites that favor atrial pacing and help reduce atrial fibrillation burden, and (4) pacing or high-voltage termination of atrial tachyarrhythmias with combined atrial and ventricular ICDs.

Pharmacologic rate control during atrial fibrillation or flutter is often inefficient or not tolerated in effective doses because of the negative inotropic effect of some of these agents. An alternative electrical treatment approach is radiofrequency catheter ablation of the atrioventricular node and permanent ventricular pacing.[51] This ablate and pace approach is nearly 100% effective in controlling the ventricular rate during atrial tachyarrhythmias; has a low procedural complication rate; and has been shown to improve symptoms, the left ventricular ejection fraction, and quality of life in most of these patients. Recently published long-term results of atrioventricular junction ablation and pacing therapy showed no increased mortality after atrioventricular junction ablation, a concern raised earlier and probably avoided by gradually decreasing the ventricular pacing rate in the first few weeks after implantation of the pacemaker.[52]

Catheter ablation for prevention (not rate control) of atrial fibrillation is currently being investigated in many centers worldwide.[53–55] Various techniques are being used, but the common feature is electrical isolation of pulmonary veins. Spontaneous activity originating in the pulmonary veins appears to play a significant role in the initiation of atrial fibrillation in most people studied, at least in the early stages.[55] The reported success rate varies significantly between 50% to 90%, depending on the population included and the techniques used. It appears, however, that the short-term success rates are lower and recurrence rates higher in patients with structural heart disease and chronic atrial fibrillation. The risk of procedural complications (mainly cardiac perforation, stroke, and pulmonary vein stenosis) is relatively high at 2% to 3%. Therefore, the role of curative atrial fibrillation ablation in patients with heart failure is limited.

Increasingly, pacing therapy is also being used to prevent episodes of atrial fibrillation. In patients with sick sinus syndrome and sinus bradycardia, atrial pacing at physiologic rates can help reduce the frequency of atrial fibrillation episodes.[56,57] Multisite atrial pacing and newer pacing algorithms, designed to ensure nearly 100% atrial pacing, have also been shown to reduce the frequency of atrial fibrillation episodes. When pacing is indicated for bradyarrhythmias, an atrial pacing approach, as opposed to ventricular-based pacing, also favors sinus rhythm.[57] Antitachycardia pacing algorithms for atrial tachyarrhythmias are now also available in patients receiving dual-chamber ICDs and select pacemaker models, and they appear to be effective in terminating atrial flutter or other stable reentrant atrial tachycardias.[58] Atrial cardioversion in patients with ICDs and atrial defibrillators have not gained widespread patient acceptance because of the discomfort associated with the shocks.

PACING IN HEART FAILURE

Cardiac output is determined by heart rate and stroke volume. During exercise, both heart rate and stroke volume increase in healthy subjects, but the increase in heart rate accounts for a greater percentage of the increase in cardiac output than does the increase in stroke volume. In patients with heart failure, cardiac reserve is diminished as a result of left ventricular dysfunction, and these patients rely to a greater extent on increments in heart rate to adjust cardiac output to increases in oxygen demand. Several heart failure medications, such as β-blockers and digoxin, can lower resting heart rate and attenuate compensatory increases in heart rate. Therefore, patients with heart

failure with spontaneous or medication-induced bradyarrhythmias may benefit from rate-supportive pacing and respond with increased cardiac output.[56] In patients with chronotropic incompetence, rate-responsive pacemakers can increase the heart rate and cardiac output during exercise. Optimizing atrioventricular delay has also been evaluated as an adjunctive strategy to improve the timing of ventricular filling and thereby improve cardiac stroke volume.[59-61] Although this measure may improve cardiac output in selected patients in the short term, long-term studies did not show sustained benefit in most patients without significant atrioventricular conduction abnormalities.

The choice of the ventricular pacing site appears to have a major impact on ventricular contraction and function. It appears that pacing from the right ventricular apex, the established pacing location for several decades, can be associated with significant deterioration of ventricular function.[62,63] Although this effect is rarely clinically relevant in the vast majority of pacemaker patients who have preserved left ventricular function, patients with heart failure may experience significant hemodynamic deterioration. Right ventricular apical pacing in patients with heart failure has been associated with a higher incidence of congestive heart failure, a decrease in left ventricular fractional shortening, increased use of diuretics, and more frequent need for cardiac transplantation. Alternative right ventricular pacing sites have not been demonstrated to be superior to right ventricular apical pacing or are technically challenging. Right ventricular septal pacing alone or as part of dual right ventricular pacing may provide a benefit in a few selected patients, but randomized trials have failed to show a benefit in larger groups.[56] Pacing at the bundle of His, which mimics intrinsic ventricular activation, showed promise in a small study, but it is technically challenging with currently available equipment.[64] Therefore, in patients with heart failure with indications for a dual-chamber pacemaker or defibrillator, right ventricular pacing should be minimized through appropriate programming as long as intrinsic conduction with physiologic intervals is present. On the other hand, left ventricular and biventricular pacing have been shown to improve left ventricular function in patients with prolonged QRS interval duration. Asynchronous ventricular contraction is emerging as a novel form of (electrical) heart failure therapy.[65] The benefits of biventricular pacing are discussed elsewhere in this supplement.[22,66]

FUTURE DIRECTIONS

Electrical therapy in patients with heart failure has been shown to improve symptoms and survival in select patient populations. Many questions remain unanswered.

Does ICD therapy reduce mortality in patients with nonischemic cardiomyopathy? Several major randomized trials designed to answer this question have completed enrollment, and results are expected in the next 2 years.[67] The Sudden Cardiac Death and Heart Failure Trial (SCD-HeFT) is an ongoing trial of 2,500 patients with NYHA class II or III heart failure and either ischemic or idiopathic dilated cardiomyopathy. Patients were randomized into 1 of 3 arms: (1) standard heart failure therapy plus placebo, (2) standard heart failure therapy plus amiodarone, or (3) standard heart failure therapy plus ICD. The primary end point is total mortality. The 2-year follow-up data from this trial will be available this year. About 50% of the included patients have nonischemic dilated cardiomyopathy.

The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) is an ongoing trial of 400 patients with nonischemic dilated cardiomyopathy, an ejection fraction <0.35, symptomatic heart failure (class II or III), and complex ventricular ectopy (>10 premature ventricular complexes per hour, nonsustained VT). Patients are being randomized to an ICD or standard care and are being observed for 2 to 3 years; the primary end point is mortality.

Should patients with recent (<4 weeks) myocardial infarction and reduced left ventricular function receive an ICD? Patients with myocardial infarction or revascularization procedures within 4 weeks of the index arrhythmia or screening were excluded from the primary prevention trials (MUSTT, MADIT I and II). Therefore, it is unknown whether ICD therapy in patients thought to be at high risk for sudden cardiac death within the first 4 weeks after an acute event will improve survival. The myocardial substrate for arrhythmias is changing mostly in the first few weeks after an acute myocardial infarction caused by reperfusion and/or remodeling, and the mechanism and prognostic significance of arrhythmias in this period may not be the same as in patients with chronic ischemic heart disease. On the other hand, the risk of sudden death is highest within the first few months after an acute ischemic event. Several ongoing trials are attempting to answer this question.[67] The Beta-blocker Strategy plus Implantable Cardioverter Defibrillator Trial (BEST) includes patients after an acute myocardial infarction, with an ejection fraction of ≤ 0.40, reduced heart rate variability, and frequent premature ventricular complexes or positive signal-averaged electrocardiography. Patients are randomized to conventional plus β-blocker therapy or electrophysiologically guided therapy. If inducible, patients receive an ICD plus β-blocker. If they are not inducible, they receive β-blocker therapy alone. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) is studying patients 6 to 21 days after an acute myocardial infarction with a heart rate >80 beats per minute or reduced heart rate variability. These patients are randomized to conventional therapy versus additional ICD therapy. Other ongoing studies (the South European Defibrillator Trial [SEDET] and the Isostent for Restenosis Intervention Study [IRIS]) have similar designs.

What is the ptimal site for ventricular pacing? In patients with heart failure with standard indications for ventricular pacing, there is increasing evidence that right ventricular pacing may worsen ventricular function and aggravate heart failure. With the emerg-

TABLE 4 Electrical Therapy in Patients with Heart Failure

Electrical Therapy	Patient Selection Criteria	Benefits/Goals
ICD	Cardiac arrest, sustained VT, VF Syncope, EF ≤0.40, inducible VT/VF Ischemic CM, EF ≤0.40, inducible VT/VF Ischemic CM, EF ≤0.30 Syncope, nonischemic CM, EF ≤0.30 Bridge to cardiac transplant	Primary and secondary prevention of sudden cardiac death
Atrial pacing (RA) ± RV pacing (AAI or DDD)	Symptomatic sinus bradycardia Sick sinus syndrome Chronotropic incompetence	Increase cardiac output at rest and/or during exercise Newer algorithms may help prevent atrial fibrillation
Dual chamber (RA + RV) pacing with optimized AV interval	Marked AV conduction delay with presystolic regurgitation	Improved left ventricular filling
AV junction ablation and ventricular pacing	Atrial fibrillation with drug-refractory rapid ventricular response	Prevent/treat tachycardia-mediated cardiomyopathy, reduce myocardial oxygen demand, improve cardiac reserve
Biventricular pacing (RA + RV + LV)	NYHA class II, III, IV; QRS duration >120 msec, LBBB, left ventricular dilatation and dyssynchrony	Improve heart failure symptoms, increase EF, improve survival (?)
Catheter ablation of supraventricular tachyarrhythmias	SVT Atrial flutter Atrial tachycardia (?) Paroxysmal atrial fibrillation	Prevent/treat tachycardia-mediated cardiomyopathy, restore atrial kick, avoid antiarrhythmic drugs with negative inotropic effects
Catheter ablation of VT	Frequent recurrent VT Bundle branch reentrant VT	Adjunctive therapy to prevent frequent shocks by ICD

AV = atrioventricular; CM = cardiomyopathy; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LV = left ventricle; NYHA = New York Heart Association; RA = right atrium; RV = right ventricle; SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

ing feasibility of transvenous pacing of the left ventricle via tributaries of the coronary sinus, future trials may show that, in patients with standard indications for ventricular pacing, left ventricular pacing will prove advantageous compared with right ventricular pacing. In the meantime, care should be taken to minimize right ventricular pacing in patients receiving dual-chamber devices who have intact atrioventricular conduction.

Which patients may be candidates for VT ablation as the sole therapy? The recurrence rate of VT in a recent trial using substrate mapping was 21% at 2 years, reflecting improvements in VT ablation methods. Conceivably, VT ablation alone may be a therapeutic option in select patients presenting with such arrhythmias, especially in patients with relatively preserved left ventricular function.

Can electrical therapy of atrial fibrillation improve morbidity and mortality compared with a rate-control approach? The recent Atrial Fibrillation Follow-up Investigation in Rhythm Management (AFFIRM) trial failed to show an improved outcome in patients with minimally symptomatic atrial fibrillation randomized to rhythm control versus rate control.[68] A potential explanation is that the pharmacologic agents and repeated cardioversion attempts are associated with increased morbidity and mortality, which may mitigate the possible beneficial effect of maintaining sinus rhythm. Whether nonpharmacologic maintenance of sinus rhythm with catheter ablation and/or pacing therapy would fare better in such a comparison remains to be determined.

Will cardiac resynchronization therapy improve survival in patients with heart failure? Cardiac resynchronization therapy has been recently shown to improve the functional status and quality of life in patients with advanced heart failure. The effect of resynchronization therapy on survival is currently under investigation; however, preliminary data support this conclusion.

CONCLUSION

In summary, electrical therapy in patients with heart failure offers many opportunities for improving symptoms and survival (Table 4). Electrical devices are available to treat atrial and ventricular tachyarrhythmias, to prevent atrial fibrillation, and to improve left ventricular dyssynchrony. Catheter ablation techniques are available to cure clinically manifest atrial tachycardias and VTs. Future devices may incorporate features designed to prevent VT and monitor hemodynamics. Careful selection of patients is essential, because effective antiarrhythmic therapy may not necessarily lead to improved survival. Given the interdependence of arrhythmias and heart failure, successful management of these patients requires close collaboration of heart failure specialists and cardiac electrophysiologists.

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